

PCT

To:

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2004/006843

International filing date (day/month/year)
24.06.2004

Priority date (day/month/year)
24.06.2003

International Patent Classification (IPC) or both national classification and IPC
C12Q1/68

Applicant
EPIGENOMICS AG

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
☒ a sequence listing
☐ table(s) related to the sequence listing
 - b. format of material:
☒ in written format
☒ in computer readable form
 - c. time of filing/furnishing:
☐ contained in the international application as filed.
☐ filed together with the international application in computer readable form.
☒ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	4,5,23-25
	No: Claims	1-3,6-22
Inventive step (IS)	Yes: Claims	
	No: Claims	1-25
Industrial applicability (IA)	Yes: Claims	1-25
	No: Claims	

2. Citations and explanations

see separate sheet

V. Reasoned statement (Continuation)

2.1 CITATIONS

Reference is made to the following documents:

- D1:** WO 02/072880 A (EPIGENOMICS AG; OLEK, ALEXANDER; BERLIN, KURT) 19 September 2002 (2002-09-19)
- D2:** WO 00/70090 A (UNIVERSITY OF SOUTHERN CALIFORNIA) 23 November 2000 (2000-11-23)
- D3:** DATABASE GENBANK US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; Accession number: M24485.1 5 December 1994 (1994-12-05), MORROW, C.S. ET AL.: "Structure of the human genomic glutathione S-transferase pi (GSTP1) gene, complete cds." XP002321758
- D4:** DATABASE GENBANK US NATIONAL LIBRARY OF MEDICINE (NLM), BETHESDA, MD, US; Accession number: AY324387 24 June 2003 (2003-06-24), RIEDER, M.J. ET AL.: "Homo sapiens glutathione S-transferase pi (GSTP1) gene, complete cds." XP002321759

2.2 NOVELTY (Art. 33(2) PCT)

- 2.2.1 **D1** discloses the content of **claims 1 - 3** and **6 - 22**, c.f. pages 7 - 31, claims 1 - 41, examples 3 - 10 and figures 10 - 13. **D2** is novelty-destroying to **claims 1, 2, 6 - 11** and **13 - 16**, c.f. pages 10 - 22, claims 1 - 26, figures 1 - 4 and examples 2 - 4.
- 2.2.2 The present application does not satisfy the criterion set forth in **Article 33(2) PCT** because the subject-matter of **claims 1 - 3** and **6 - 22** is not new in respect of prior art as defined in the regulations (**Rule 64(1)-(3) PCT**).

2.3 INVENTIVE STEP (Art. 33(3) PCT)

2.3.1 Document **D1** is considered to represent the most relevant state of the art for **claims 1 - 24** and discloses a method for the detection of cytosine methylation in DNA samples and more particularly a heavymethyl assay for the methylation analysis of the GSTPI gene, characterized in the steps outlined in claim 1 of the underlying application, c.f. pages 7 - 31, claims 1 - 41, examples 3 - 10 and figures 10 - 13.

2.3.2 The subject-matter of **claims 1 - 24** differs with respect to the primer sequences used to undergo the methylation specific PCR and in particular with respect to the sequence identity number mentioned in dependent claims 4 and 5.

2.3.3 The problem to be solved by the subject matter of claim **claims 1 - 24** may therefore be regarded as providing alternative primer specificities for use in a heavymethyl assay for the methylation analysis of the GSTPI gene.

2.3.4 The solution would be the provision of the primer specificities / sequence identity numbers mentioned in **claims 3 and 4**.

2.3.5 This solution cannot however be considered as involving an inventive step (**Article 33(3) PCT**) for the following reasons:

2.3.5.1 According to the applicant, the primer specificities / sequence identity numbers mentioned in claims 3 and 4 are entirely derived from 2 data base deposits cited by the applicant in the underlying application as **D3** and **D4**, c.f. page 6, second paragraph of the underlying application. The design of primers suitable in the polymerase chain reaction technology though is a matter of routine practicing and the selection of particular primers designed from a known sequence data base deposit can only be regarded as inventive, if these primers present unexpected effects or properties in relation to the rest of the range. However, no such effects or properties are indicated in the application. Hence, no inventive step is present in the subject-matter of **claims 1 - 24**.

2.3.5.2 The product claim of **claim 25** cannot be inventive either: a kit comprising two particular oligonucleotides solves no problem and therefore does not provide a solution even in the case that the sequence context (e.g. the data base deposits

of **D3** and **D4**) had not been known from the prior art.

- 2.3.6 The present application does therefore not satisfy the criterion set forth in **Article 33(3) PCT** and the subject-matter of **claims 1 - 25** does not involve an inventive step (**Rule 65(1)(2) PCT**).